Remarks

Claims 1-12 and 14-56 are pending upon entry of the foregoing amendments.

I. Amendments to the Claims

Claim 1 has been amended to clarify that Applicants' microparticles have pores that are defined by a structural material, that the structural material includes the hydrophobic matrix material and the pharmaceutical agent, and that the pharmaceutical agent is dispersed in the hydrophobic matrix material. That is, claim 1 as amended makes unmistakable that the pharmaceutical agent is part of that which *defines* the void spaces of the microparticle; it is not *in* the void space of the microparticle.

Support for the amendment is explicitly and implicitly found throughout Applicants' specification. See, for example, page 12, lines 15-19 ("The porous microparticles comprise a matrix material and a pharmaceutical agent. ... the term "matrix" refers to a structure including one or more materials in which the pharmaceutical agent is dispersed, entrapped, or encapsulated. The matrix is in the form of porous microparticles.) See also pages 10-12, which includes a description of how porosity is calculated, which necessarily requires the pores to be open, i.e., unoccupied by drug, matrix, or other structural material. Unlike DeLuca's "pores" which are filled with the drug or other "incorporated agent", Applicants' pores—by definition—would not consider such filled space to be pores. In this way, it is clear that claim 1 does not cover the arrangement of materials disclosed by the DeLuca reference, i.e., where the drug is confined in the "pores."

Claim 50 has been amended to specify that the pharmaceutical agent is *dispersed* in the matrix material, making the claim language consistent with other independent claims.

II. Rejection Under 35 U.S.C. § 103

Claims 1-12 and 14-56 are rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 4,818,542 to DeLuca et al. ("DeLuca") in view of U.S. Patent No. 6,395,300 to Straub et al. ("Straub"). The rejections are respectfully traversed, for the reasons of record and additional reasons articulated below.

A. Applicants' Claimed Subject Matter

Most pharmaceutical agents delivered by inhalation are *immediate* release formulations that must be inhaled multiple times per day, which discourages patient compliance (Pg. 1, Lns. 17-19). The frequent inhalation dosing of immediate release formulations leads to pharmaceutical agent levels that peak and trough, causing undesirable toxicity or inadequate efficacy (Pg. 1, Lns. 19-21). In contrast with these typical formulations, Applicants have discovered and teach how to select a particular combination of microparticle size, porosity, and composition able to release the pharmaceutical agent for a desired *sustained* period (Pg. 9, Lns. 11-12). The formulations enable one to avoid undesirable burst effects yet can release the majority of the pharmaceutical agent before the microparticles are removed by the pulmonary clearance mechanisms. This advantageously can provide a less fluctuating, more constant concentration of pharmaceutical agent—highly important in the delivery of pharmaceuticals (Pg. 7, Lns. 7-11).

Independent claim 1 is directed to a sustained release pharmaceutical formulation for delivery to the lungs of a patient by inhalation. The formulation comprises porous microparticles that have voids defined by a structural material which comprises a pharmaceutical agent dispersed in a hydrophobic matrix material. The microparticles have a geometric size between

0.1 μm and 5 μm and an average porosity between 15 % and 90 % by volume. The combination of the pharmaceutical agent, matrix material, geometric size, and average porosity provides that, upon inhalation of the formulation into the lungs, a therapeutically or prophylactically effective amount of the pharmaceutical agent is released from the microparticles in the lungs for at least 2 hours.

B. Relevant Law on Obviousness

The Patent Office bears the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103(a). A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a) (2007). In its recent decision pertaining to the assessment of obviousness, *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1734 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; (4) objective evidence of nonobviousness. In an obviousness inquiry, every limitation of the invention at issue must be found to exist in the prior art references.

Section 2143 of the M.P.E.P. sets forth various rationales by which an Examiner, following *KSR*, may set forth a *prima facie* case of obviousness. While the various rationales may differ in specificity, each still places the burden squarely upon the Examiner to produce evidence sufficient to form a *prima facie* case of obviousness. If the Examiner fails to set forth

such evidence, the Applicant is under no obligation to set forth rebuttal evidence of nonobviousness. *See* M.P.E.P. at § 2142.

Obviousness of a claim may not be proved "merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S.Ct. at 1741. Instead, it is necessary to identify some "apparent reason to combine the known elements." *Id.* at 1740. That reason should not merely be the result of the Examiner having read Applicants' specification and then using "the inventor's disclosure as a blueprint for piecing together the prior art." *Iron Grip Barbell Co. v USA Sports, Inc.*, 392 F.3d 1317, 1320 (Fed. Cir. 2004).

C. The Primary References

1. DeLuca

DeLuca's invention is "to provide porous microsphere matrices wherein the accessability of the drug ... is not dependent upon the physical or chemical erosion of the polymer for release [of the drug]." (Col. 2, Lns. 64-68) (emphasis added). According to DeLuca, "the necessity for biodegradation or bioerosion of the polymer matrix is obviated by reason of the intrinsic porosity characteristics of the polymer matrices of the invention and the fact that the incorporated agent or agents are matrix confined within the interconnecting channels or pores of the spherical polymer" (Col. 5, Lns. 15-22) (emphasis added). The selection of the matrix material therefore would not impact how the release of drug is controlled.

DeLuca teaches that the "location of the agent [is] confined essentially completely inside the pores of the porous microspheres of the invention" (Col. 6, Lns. 20-24) (emphasis added). The methods for preparing the drug delivery systems create microspheres "wherein the incorporated agent is confined within the walls and channels of the pores as opposed to random

distribution within the more poorly defined interstices of the polymer" (Col. 6, Lns. 15-19) (emphasis added). Hence, DeLuca himself does *not* consider the drug to be "dispersed" within the matrix material. In sum, DeLuca discloses that the incorporated agent is not part of the structure of the wall forming material, but rather is confined to the interior surface of the pores or channels in the structure, such that the release kinetics of drug **are independent** of degradation of the polymer matrix material.

2. Straub

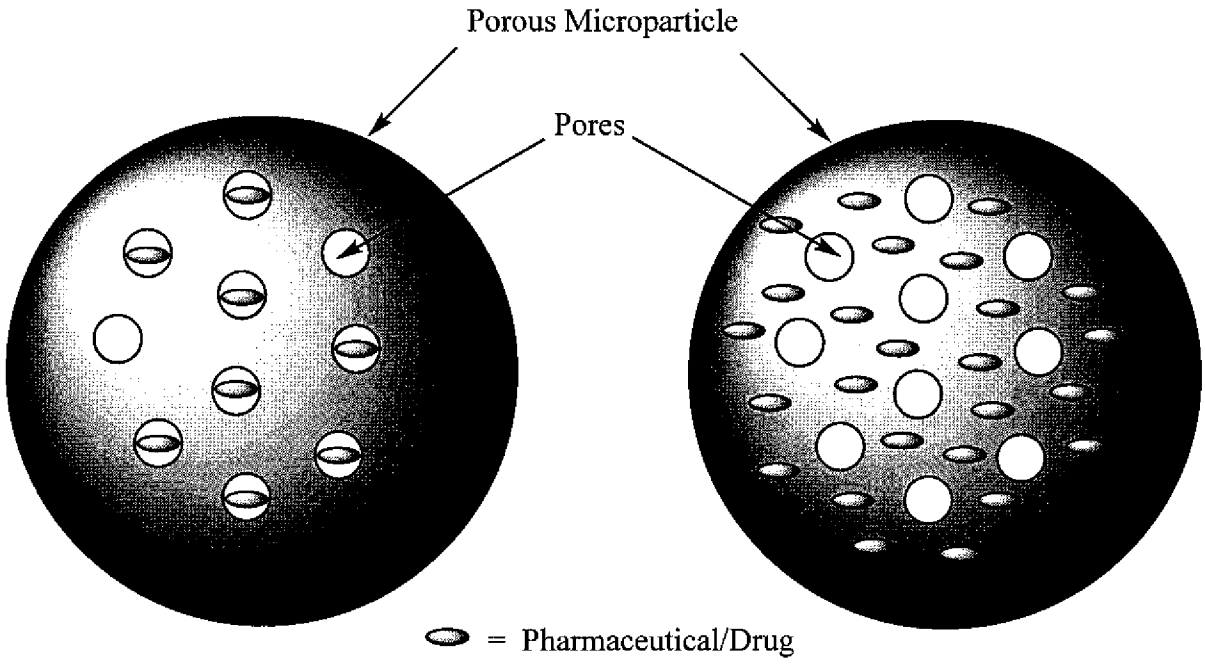
Straub discloses that drugs, especially low aqueous solubility drugs, can be provided in microparticles so as to *enhance* the dissolution of the drug (Abstract). In order to speed up drug release, Straub specifies the use of drug matrices that include *hydrophilic* excipients and *hydrophilic* polymers (Col.8, Lns. 11 and 36). These *hydrophilic* materials allow water to penetrate the matrices and *increase* the dissolution of the drug (Col. 8, Lns. 14-21). Straub is directed to *increasing* the rate of release of a hydrophobic drug that otherwise might not release in a therapeutically effective amount. Straub therefore teaches that the release kinetics of the drug **are dependent** on matrix material.

D. The Examiner's Ascertainment of the Differences Between DeLuca and Applicants' Claims is Inaccurate.

At page 6 of the Office Action mailed June 5, 2008, the Examiner contents that "DeLuca incorporates the agent into the pores of the particle" and that "it is therefore understood by the examiner that this is a form of encapsulation. The dispersion limitation is supported by the fact that the pores are contained throughout the particle, not limited to the surface of the particle." The Examiner's comparison of Applicants' claims with DeLuca is flawed, because the three

parts—matrix material, drug, and pores—forming the microparticles are in entirely distinct arrangements, as illustrated schematically in Figure A below.

Figure A



All of Applicants' independent claims as written necessarily avoid reading on DeLuca. For example, unlike Applicants' claim 1, DeLuca fails to disclose or suggest porous microparticles wherein the structural material defining and bounding the voids of the microparticle comprises a pharmaceutical agent dispersed in a hydrophobic matrix material. DeLuca specifies that the drug is confined to the pores, so it cannot be dispersed in the structural material defining the pores. Furthermore, unlike Applicants' claims 1, 3, 31, 32, 33, 46, and 50, DeLuca's microspheres do not have pharmaceutical agent *dispersed and encapsulated* in the

hydrophobic matrix material, because DeLuca expressly teaches that the **drug is <u>not</u> distributed in the polymer.** *See* Col. 6, Lns. 15-19.

The Examiner's reading of Applicants' claims is unreasonably broad and contrary the art. It is improper to construe DeLuca to teach Applicants' claim feature that the pharmaceutical agent is "dispersed and encapsulated within the hydrophobic matrix material" when DeLuca expressly teaches that it is not. Furthermore, the Examiner's argument that the pores extend into the microsphere is irrelevant because although DeLuca's drug may be distributed in pores throughout the *microsphere*, it is neither encapsulated nor dispersed within the *matrix material*. One skilled in the art would not confuse those distinct concepts. And one skilled in the art would not, as the Examiner has done, effectively read the term "dispersed and encapsulated" out of its context with the immediately following phrase "within the hydrophobic matrix material."

E. Applicants' Claims Are Patentable over DeLuca and Straub.

1. The Examiner Failed to Identify Sufficient Rationale to Support a *Prima Facie* Case of Obviousness.

In rejecting these claims, the Examiner alleges that DeLuca's teaching of porous microspheres wherein the drug is imbedded in the pores provides the skilled artisan with the motivation to alter the number of pores on the microparticles to attain Applicants' drug release profile, and combine the excipients of Straub's porous microparticle composition with the composition of DeLuca. The Examiner presents three arguments why the combination of DeLuca and Straub is allegedly proper. Whether taken separately or together, none of Examiner's arguments have merit. The rejection should be withdrawn because DeLuca and Straub do not, singly or in combination, teach, suggest, or describe the claimed invention.

First, the Examiner argues that "[t]he determination of the average porosity volume would have been obvious to one of ordinary skill in the art" based on DeLuca (Office Action, p. 5). The Examiner contends that:

> "[o]ne of ordinary skill in the art when formulating a porous particle for the sustained release of a drug would have determined that the amount of pores on the particles would have an effect on the delivery of the drug; the more pores the greater the delivery of the drug over a period of time; the less amount of pores, the less delivery of the drug over the same period of time" (Office Action, p. 5).

This statement is misleading because DeLuca does not teach anything about manipulated porosity to control release kinetics. In fact, DeLuca's description of "pore" volume does not appear to have any correlation to actual porosity. For example, DeLuca teaches in Example 4 that the "void" space of the porous spheres is 94.5% which is equal to the fraction of solvent in the dispersed phase. (Col. 10, Ln. 55 to Col. 11, Ln. 3). This cannot reasonably be considered an accurate assessment of porosity of the final microspheres because (1) it neglects that the likely collapse of void spaces in the polymer as solvent is removed, and (2) Figure 14A shows the resulting microspheres which look fairly solid, which would not be consistent with a 94.5% porosity.

Second, the Examiner argues that "[a]lthough . . . DeLuca et al. do not teach the agent being released from the microparticles in the lungs for at least 2 hours as claimed by applicant, it is the position of the examiner that this limitation would be met as DeLuca et al. teach the claimed invention" (Office Action, p. 4). This rationale fails because the Examiner presents no evidence or citations to the prior art of record to support the conclusion. As detailed above, the structural differences between DeLuca's microspheres and Applicants' claimed microparticles

weigh against the Examiner's bare assertion. DeLuca does not teach or suggest Applicants' claimed release profile or how to select the combination of the pharmaceutical agent, matrix material, geometric size, and average porosity to control release rate.

The Examiner alleges that "there is no additional information in the specification with regards to the release profile (i.e. coating or physical makeup which makes it a sustained release)" (Office Action, p. 5). This is false. Contrary to Examiner's assertion, detailed information regarding the physical makeup that allows Applicants' methods and formulations to achieve the claimed release profile can be found, for example, at page 7, lines 7-20 and page 10, lines 14-24:

> ... it has been discovered that the composition of the microparticles (e.g., the matrix material, surfactant) can be selected to provide delayed release (and avoid the burst effect associated with immediate release formulations), and the porosity of the microparticles can be selected to provide the majority of the pharmaceutical agent release before the microparticles are removed by the pulmonary clearance mechanisms. Although the composition of the microparticles can be selected to slow the release of the pharmaceutical agent, selection of the composition alone may not ensure that a sufficient amount of pharmaceutical agent is released before the microparticles are removed by the pulmonary clearance mechanisms. For a given composition of the microparticles, the porosity can be selected to ensure that a therapeutically or prophylactically effective amount of the pharmaceutical agent continues to be released after 2 hours, preferably such that a majority (e.g., more than 50%, more than 75%, more than 90% by weight of the pharmaceutical agent) of the pharmaceutical agent is released from the microparticles by 24 hours following inhalation.
>
> ....
>
> For a given microparticle composition (pharmaceutical agent and matrix material) and structure (microparticle porosity and thus density) an iterative process can be used to define where the microparticles go in the lung and the duration over which the microparticles release the pharmaceutical agent: (1) the matrix material, the pharmaceutical agent content, and the microparticle geometric size are selected to determine the time and amount of initial pharmaceutical agent release; (2) the porosity of the microparticles is selected to adjust the amount of initial pharmaceutical agent release, and to ensure that significant release of the pharmaceutical agent occurs beyond the initial release and that the majority of the pharmaceutical agent release occurs within 24 hours; and then (3) the geometric particle size and the porosity are adjusted to

> achieve a certain aerodynamic diameter which enables the particles to be deposited by inhalation to the region of interest in the lung.

Moreover, Applicants' Example 4 show that sustained release of a drug has been demonstrated *in vivo*, from particles administered to the lungs of human subjects. In contrast, DeLuca fails to provide any teaching about how to deliver a therapeutically or prophylactically effective amount of a drug from microspheres in the lungs for at least 2 hours.

A *prima facie* case of obviousness requires more than a mere suggestion of trying to solve the same problem, particularly where there are a myriad of possible paths to explore for the solution. A person of ordinary skill in the art trying to alter the release profile —the problem posited by Examiner—has numerous technical options to choose from in trying to meet such an objective. For example, DeLuca teaches that the matrix may be coated with a film or cross-linking agent to inhibit or control release rates (Column 5, Lines 24-26 and 30-34). Also, as noted above, DeLuca teaches that the selection of the matrix material would not control the release of pharmaceutical agent because of the pore-incorporated design. In contrast, Applicants' sustained release methods and compositions are achieved by selecting combinations of particle size, porosity, and composition. Therefore, one of ordinary skill in the art would not have been led from DeLuca to derive Applicants' claimed methods and formulations. Motivation to achieve a particular result should not be confused with a teaching of *how* to achieve that result.

Third, one of ordinary skill in the art would be led away from combining DeLuca and Straub, because neither would be operable as intended if combined. When applying 35 U.S.C. § 103, "the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references *must be considered as whole* and must suggest the

desirability and thus the obviousness of making the combination." *Hodosh v. Block Drug Co.*, 786 F.2d 1136, 1143 n.5 (emphasis added). Furthermore, "[a]ll evidence bearing on the issue of obviousness... must be considered and evaluated **before** the required legal conclusion is reached. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1555 (emphasis added). Thus, "[a] prior reference must be considered in its entirety, i.e. as a whole, **including portions that would lead away from the claimed invention**." M.P.E.P. § 2141.02 [VI] (emphasis added).

One of ordinary skill in the art would not want to combine DeLuca with Straub because DeLuca teaches that the incorporated agent is confined to the pores of the microsphere such that release of the incorporated agent is independent of the composition of the matrix material, whereas Straub teaches that the incorporated agent is dispersed within hydrophilic matrix materials such that release of the incorporated agent occurs immediately and is dependent upon the composition of the matrix material. One of ordinary skill in the art would not want to combine them because they teach opposing microparticle constructions and opposing operational theories. The references are incompatible, and would not lead one of ordinary skill in the art to develop Applicants' claimed microparticles for sustained release. In fact, one of ordinary skill in the art would not consider Straub's *immediate* release formulations at all if trying to make a *sustained* release formulation.

Even if taken together, Examiner's arguments do not cumulatively amount to a *prima facie* case of obviousness. Across the board, Examiner (i) failed to set forth any sound motivation for combining DeLuca and Straub, (ii) failed to provide any explanation for how the composition of DeLuca may achieve the release profile of Applicants' composition, and (iii) failed to set forth any reason why a person of skill in the art would look to Straub. The Supreme

Court in *KSR* stated that mere conclusory statements by an Examiner cannot support a *prima facie* case of obviousness. *KSR*, 127 S.Ct. at 1741 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinnings to support the legal conclusion of obviousness."). *See also* M.P.E.P. § 2143.01 (IV).

For the foregoing reasons, it is respectfully submitted that a proper *prima facie* case of obviousness has not been made for the present claims.

2. Even if the Examiner Set Forth a Prima Facie Case, Applicants' Claims Are Patentable Because DeLuca And Straub Teach Away from Applicants' Invention.

Even if DeLuca and Straub are considered together, the teach away from Applicants' claimed methods and formulations. First, DeLuca teaches away from Applicants' microparticles in which the pharmaceutical agent is *dispersed and encapsulated* within the hydrophobic matrix material, because DeLuca teaches that with its invention "the incorporated agent is confined within the walls and channels of the pores as opposed to random distribution within the more poorly defined interstices of the polymer." (Col. 6, Lns. 15-19). Second, Straub teaches away from Applicants' *sustained release* microparticles in which the pharmaceutical agent is dispersed and encapsulated within the *hydrophobic* matrix material, because Straub teaches the use of the *hydrophilic* matrices materials in order to *increase* the rate of drug release.

It is improper for the Examiner to ignore these teachings of DeLuca and Straub that are contrary to the structure, composition, and purpose of Applicants' claimed invention. "A prior reference must be considered in its entirety, i.e. as a whole, *including portions that would lead away from the claimed invention*." M.P.E.P. § 2141.02 [VI] (emphasis added). One of ordinary

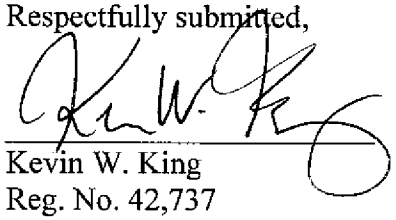
skill would have been unmotivated to consider these references alone or in combination in a manner consistent with that which is Applicants claim. Accordingly, any alleged *prima facie* case is rebutted.

III. Conclusions

Applicants respectfully submit that claims 1-12 and 14-56 are non-obvious and patentable over the prior art of record. Allowance of all pending claims is therefore earnestly solicited.

The undersigned invites the Examiner to contact him by telephone (404.853.8068) if any outstanding issues can be resolved by conference or examiner's amendment.

Respectfully submitted,



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